REMARKS

Claims 123-164 were pending in the subject application of which claims 126, 129-132, 137, 140-143, 148, 151-154, 158 and 161-164 were indicated to be allowable in the December 30, 2004 Office Action. By this Amendment, applicants have amended independent claim 123 to incorporate the allowable subject matter of claim 126; amended independent claim 134 to incorporate the allowable subject matter of claim 137; amended independent claim 145 to incorporate the allowable subject matter of claim 148; and amended independent claim 155 to incorporate the allowable subject matter of claim 158. Applicants have also amended dependent claims 129-130, 133, 140-141, 144, 151-152 and 161-162 and canceled claims 124-126, 135-137, 146-148 and 156-158. Accordingly, claims 123, 127-134, 138-145, 149-155 and 159-164 are pending in the subject application.

Support for the amendment to claim 123 may be found *inter alia* on page 3, lines 17, 18-19, and 28-30 of the subject application.

Support for the amendment to claim 129 may be found *inter alia* on page 12, lines 10-14 of the subject application.

Support for the amendment to claim 130 may be found *inter alia* on page 23, lines 3-30 of the subject application.

Support for the amendment to claim 133 may be found *inter alia* in column 2, lines 40-43 of U.S. Patent No. 5,800,808, the relevant text of which has been incorporated into the subject application by a previous amendment and on page 32,

lines 15-16 of the subject application.

Support for the amendment to claim 134 may be found *inter alia* on page 3, lines 17, 18-19, and 28-30 of the subject application.

Support for the amendment to claim 140 may be found *inter alia* on page 12, lines 10-14 of the subject application.

Support for the amendment to claim 141 may be found *inter alia* on page 23, lines 3-30 of the subject application.

Support for the amendment to claim 144 may be found *inter alia* in column 2, lines 40-43 of U.S. Patent No. 5,800,808, the relevant text of which has been incorporated into the subject application by a previous amendment and on page 32, lines 15-16 of the subject application.

Support for the amendment to claim 145 may be found *inter alia* on page 3, lines 17, 18-19, and 28-30 of the subject application.

Support for the amendment to claim 150 may be found *inter alia* on page 3, lines 30-31 of the subject application.

Support for the amendment to claim 151 may be found *inter alia* on page 12, lines 10-14 of the subject application.

Support for the amendment to claim 152 may be found *inter alia* on page 23, lines 3-30 of the subject application.

Support for the amendment to claim 155 may be found *inter alia* on page 3, lines 17, 18-19, and 28-30 of the subject application.

Support for the amendment to claim 161 may be found *inter alia* on page 12, lines 10-14 of the subject application.

Support for the amendment to claim 162 may be found *inter alia* on page 23, lines 3-30 of the subject application.

Applicants are pleased to note that on page 2, section 2 of the December 30, 2004 Office Action, the Examiner stated that Group I and II (claims 123-164) have been rejoined and all pending claims have been examined.

On page 2, section 4 of the December 30, 2004 Office Action, the Examiner objected to the abstract of the disclosure because it is more than one paragraph and required correction, citing MPEP §608.01(b).

In response, applicants have amended the Abstract of the disclosure to be one paragraph that does not exceed 150 words.

On page 2, section 5 of the December 30, 2004 Office Action, the Examiner advised applicants to amend the first paragraph of the specification to update the relationship between the instant application and U.S. Serial No. 09/816,989 filed March 23, 2001, which is now U.S. Patent No. 6,800,287.

In response, the applicants have amended the first paragraph of specification to reflect the relationship between the

subject application and U.S. Patent No. 6,800,287.

Rejections under 35 U.S.C. §112, second paragraph

On page 3, section 8 of the December 30, 2004 Office Action, the Examiner rejected claims 123, 134, 145 and 155 under 35 U.S.C. §112, second paragraph, as allegedly being incomplete for omitting essential steps, such omission amounting to a gap between the steps, citing MPEP § 2172.01. The Examiner alleged that the omitted steps in claims 123, 134, 145 and 155 are the defined average molecular weight of the polypeptides, the amino acid sequences of the polypeptides, and the desired molecular weight of the polypeptides/markers to be included in the pharmaceutical product for the claimed process.

In response, applicants respectfully submit that claims 123, 134, 145 and 155 do not omit essential material because the claims specify that the polypeptides have a "desired molecular weight" or a "predetermined sequence". However, to expedite prosecution, the applicants have amended claims 123, 134, 145 and 155 to better define their invention. Applicants have incorporated into claims 123, 134, 145 and 155 the subject matter of claims which has been indicated as allowable. Applicants respectfully submit that as amended claims 123, 134, 145 and 155 are in compliance with 35 U.S.C. §112, second paragraph.

Accordingly, applicants request that the Examiner reconsider and withdraw the rejection of claims 123, 134, 145 and 155 under 35 U.S.C. §112, second paragraph.

Rejections under 35 U.S.C. §102

On page 3, section 10 of the December 30, 2004 Office Action, the Examiner rejected claims 123-125, 127-128, 133-136, 138-139, 145-147, 149-150, 155-157 and 159-160 under 35 U.S.C. §102(b) as allegedly anticipated by U.S. Patent No. 5,800,808 ("the '808 patent") as evident by the Pharmacia Biotech Directory, citing pages 340-341.

The Examiner alleged that the '808 patent teaches a process for obtaining a pharmaceutical product containing an aqueous mixture of polypeptides each of which consists of essentially of alanine, glutamic acid, tyrosine and lysine wherein the reference mixture has a desired average molecular weight of about 4,000-8,600 Dalton which is within the claimed average molecular weight from 4000 to 13,0000 Daltons, citing col. 2, lines 8-14, in particular. The Examiner also alleged that during the process, a batch of the reference aqueous mixture of polypeptides is chromatograph on a column to such as Fractogel TSK and Superose 12 column, citing col. 3, line 6-8, to establish a relationship between retention time on the column and the molecular weight (see paragraph bridging cols 2-3, in particular). The Examiner further alleged that the reference's Superpose 12 column inherently comprises a cross-linked agarose-based medium, with an exclusion limit of 2×10^6 Daltons, an optimal separation range of 1000 to $3x\ 10^5$ Daltons and a bead diameter of 20-40 μm based on average molecular weight of the reference 4,000-8,600 Daltons which is within the claimed average molecular weight from 4000 to 13,000 Daltons and as evident by evidentiary reference Pharmacia Biotech Directory, citing page 341, in particular. The Examiner also alleged that the reference's

process of obtaining the reference pharmaceutical product is by column chromatography of L-GLAT to obtain the desired average of molecular weight species, citing the Summary of Invention section, in particular.

In response, applicants point out that the '808 patent does not disclose a plurality of molecular weight markers each of which is a polypeptide consisting essentially of alanine, glutamic acid, tyrosine and lysine and having a predetermined amino acid sequence. Therefore, applicants maintain that the '808 patent does not anticipate applicants' invention.

However, to expedite the prosecution of the subject application, the applicants have incorporated into claims 123, 134, 145 and 155 the subject matter of claims which has been indicated as allowable, and have canceled claims 124-125, 135-136, 146-147, and 156-157. On page 6, section 15 of the December 30, 2004 Office Action, the Examiner indicated that claims 126, 137, 148 and 158 would be allowed if rewritten in independent form including all the limitations of their base claims and any intervening claims. As noted above, amended independent claims 123, 134, 145 and 155 include the limitations of allowable claims 126, 137, 148 and 158.

Accordingly, applicants request that the Examiner reconsider and withdraw the rejection of claims 123, 128, 133-134, 138-139, 145, 149-150 and 155 under 35 U.S.C. §102(b) as being anticipated by the '808 patent.

On page 4, section 11 of the December 30, 2004 Office Action, the Examiner rejected claims 123-125, 133-136 and 144 under 35 U.S.C. §102(e) as allegedly anticipated by U.S. Patent No. 5,858,964 ("the '964 patent").

The Examiner alleged that the '964 patent teaches a process for obtaining a pharmaceutical product containing an aqueous mixture of polypeptides each of which consists of essentially of alanine, glutamic acid, tyrosine and lysine wherein the reference mixture has a desired average molecular weight of about 4,000-12,000 which is within the claimed average molecular weight from 4000 to 13,000 Daltons, citing the Summary of Invention section, col.3, lines 1-4, in particular. The Examiner alleged that the reference's process of obtaining the reference pharmaceutical product is by column chromatography of L-GLAT to obtain the desired average of molecular weight species, citing column 4, lines 8-10. The Examiner also alleged that the step of calibrating the molecular weight obtained using the column chromatography is inherent in the reference process given that the reference method produces the same desire molecular weight. The Examiner further alleged that the reference polypeptide is copolymer-1, which is also known as glatiramer acetate, citing column 2, lines 18-21. The Examiner also alleged that the reference's process further comprises a step of lyophilized the reference glatiramer acetate, citing column 4, line 35-36. Thus, the Examiner concluded that the reference teachings anticipate the claimed invention.

In response, applicants point out that the '964 patent does not disclose the use of a plurality of molecular weight

markers each of which is a polypeptide consisting essentially of alanine, glutamic acid, tyrosine and lysine and having a predetermined amino acid sequence. Therefore, applicants maintain that the '964 patent does not anticipate applicants' invention.

However, to expedite the prosecution of the subject application, the applicants have incorporated into claims 123 and 134, the subject matter of claims which has been indicated as allowable, and have canceled claims 124-125, and 135-136. On page 6, section 15 of the December 30, 2004 Office Action, the Examiner indicated that claims 126 and 137, would be allowed if rewritten in independent form including all the limitations of their base claims and any intervening claims. As noted above, amended independent claims 123 and 134 include the limitations of allowable claims 126 and 137.

Accordingly, applicants request that the Examiner reconsider and withdraw the rejection of claims 123, 133-134 and 144 under 35 U.S.C. §102(e) as being anticipated by the '964 patent.

On page 5, section 14 of the December 30, 2004 Office Action, the Examiner rejected claims 123, 127-128, 134, 138-139, 145, 149-150, 155, and 159-160 under 35 U.S.C. 103(a) as allegedly unpatentable over the '964 patent in view of Pharmacia Biotech Directory, citing pages 340-341. The Examiner stated the teachings of the '964 patent have been discussed supra.

The Examiner alleged that the invention in claims 127, 138, 149 and 159 differs from the teachings of the references only in that the process for obtaining a pharmaceutical product wherein the gel permeation chromatography column comprises a cross-linked agarose-based medium, with an exclusion limit of 2 x 10^6 Daltons, an optimal separation range of 1000 to 3x 10^5 Daltons and a bead diameter of 20-40 μm.

The Examiner alleged that the invention in claims 128, 139, 150, and 160 differs from the teachings of the references only in that the process for obtaining a pharmaceutical product wherein the gel permeation chromatography column is Superose 12.

The Examiner also alleged that Pharmacia Biotech Directory teaches a process of separating peptide based on sized using a Superose column such as Superpose 12 that is a media that provides high resolution gel filtration at rapid flow rates in a wide range of buffer conditions, citing page 340, column 1. The Examiner further alleged that the reference gel permeation chromatography column is a cross-linked agarose-based medium with an exclusion limit of 2 x 10^6 Daltons, and has an optimal separation range of 1000 to 3x 10^5 Daltons and a bead diameter of 20-40 μm citing page 341, far right column. The Examiner alleged that the reference further teaches that the highly cross-linked agarose structure of Superose is suitable for separation, purification and molecular weight determination of proteins, peptides and nucleic acid, citing page 340, column 1, first paragraph.

The Examiner alleged it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the chromatography column as taught by the '964 patent for the Superose column as taught by Pharmacia Biotech Directory for a method of obtaining a pharmaceutical product based on size exclusion as taught by the '964 patent and Pharmacia Biotech Directory. The Examiner also alleged that from the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

The Examiner also alleged that one having ordinary skill in the art would have been motivated to do this because the Pharmacia Biotech Directory teaches that the highly cross-linked agarose structure of Superose is suitable for separation, purification and molecular weight determination of proteins, peptides and nucleic, citing page 340, column 1, first paragraph. The Examiner further alleged that the '964 patent teaches the desired average of molecular weight of copolymer-1 or glatiramer acetate that consists of essentially of alanine, glutamic acid, tyrosine and lysine as a pharmaceutical product is about 4,000-12,000 which is within the claimed average molecular weight from 4000 to 13,000 Daltons, citing the Summary of Invention section, column 3, lines 1-4.

In response, applicants point out that neither the '964 patent nor Pharmacia Biotech Directory alone or in combination teaches or suggests a plurality of molecular weight markers each of which is a polypeptide consisting essentially of alanine, glutamic acid, tyrosine and lysine

and having a predetermined amino acid sequence. One skilled in the art would have no expectation of success of using a plurality of molecular weight markers of the subject invention for the calibration of a chromatography column based on the disclosures of the '964 patent and Pharmacia Biotech Directory. Therefore, applicants' invention is not obvious over the '964 patent in view of Pharmacia Biotech Directory.

However, to expedite the prosecution of the subject application, applicants have incorporated into independent claims 123, 134, 145 and 155 the subject matter of claims which has been indicated as allowable. On page 6, section 15 of the December 30, 2004 Office Action, the Examiner has indicated that claims 126, 137, 148 and 158 would be allowed if rewritten in independent form including all the limitations of their base claims and any intervening claims. As noted above, amended independent claims 123, 134, 145 and 155 include the limitations of claims 126, 137, 148 and 158.

Accordingly, applicants request that the Examiner reconsider and withdraw the rejection of claims 123, 127-128, 134, 138-139, 145, 149-150, 155 and 159 under 35 U.S.C. §103(a) as being unpatentable over the '964 patent in view of Pharmacia Biotech Directory.

On page 6, section 15 of the December 30, 2004 Office Action, the Examiner objected to claims 126, 129-132, 137, 140-143, 148, 151-154, 158, and 161-164 as being dependent upon a rejected base claim. However, the Examiner stated that these claims would be allowable if rewritten in independent form including all of the limitations of the

base claim and any intervening claims.

As noted above, applicants have canceled claims 124-126, 135-137, 146-148 and 156-158 and amended claims 123, 134, 145 and 155 to incorporate the allowable subject matter of claims 126, 137, 148 and 158. Applicants therefore request that the Examiner reconsider and withdraw the objections of claims 129-132, 140-143, 151-154 and 161-164.

SECOND SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT PURSUANT TO 37 C.F.R. §1.97(c)(2)

In accordance with their duty of disclosure under 37 C.F.R. §1.56, applicants would like to direct the Examiner's attention to the following publications which are listed again on the attached Form PTO-1449 **(Exhibit A)**. Copies of Reference Items 16-37, **(Exhibits 1-22)** are also enclosed.

1. U.S. Patent No. 4,129,666, issued December 12, 1978 to Wizerkaniuk;

2. U.S. Patent No. 5,965,600, issued October 12, 1999 to Sato, et al.;

3. U.S. Patent No. 6,024,981, issued February 15, 2000 to Khankari, et al.;

4. U.S. Patent No. 6,162,800, issued December 19, 2000 to Dolle, et al.;

5. U.S. Patent No. 6,514,938, issued February 4, 2003 to Gad, et al.;

6. U.S. Patent No. 6,620,847, issued September 16, 2003 to Konfino, et al.;

7. U.S. Patent No. 6,800,285, issued October 5, 2004 to Rodriguez, et al.;

8. U.S. Patent No. 6,800,287, issued October 5, 2004 to Gad, et al.;

9. U.S. Patent No. 6,844,314, issued January 18, 2005 to Eisenbach-Schwartz, et al.;

10. U.S. Patent Application Publication US-2002-0077278, published June 20, 2002 (Yong et al.);

11. U.S. Patent Application Publication US-2002-0055466, published May 9, 2002 (Aharoni, et al.);

12. U.S. Patent Application Publication US-2003-0170729, published September 11, 2003 (Klinger, Ety);

13. U.S Patent Application Publication No. US-2004-0106554 A1, published June 3, 2004 (Konfino, et al.);

14. U.S. Patent Application Publication No. US 2005-0014694, published January 20, 2005 (Yong, et al.);

15. U.S. Patent Application Publication No. US 2005-0019322, published January 27, 2005 (Rodriguez, et al.);

16. PCT International Application No. PCT/US00/14902 (WO 01/85797), published November 15, 2001 (Rodriguez, et al.)(**Exhibit 1**);

17. PCT International Publication No. WO 02/076503, (PCT/US01/19584), published October 3, 2002 **(Exhibit 2)**;

18. PCT International Publication No. WO 03/048735, (PCT/US02/38859), published June 12, 2003 **(Exhibit 3)**;

19. Aharoni, et al., "Copolymer 1 induces T cells of the T helper type 2 that crossreact with myelin basic protein and suppress experimental autoimmune encephalomyelitis", Proc. Natl. Acad. Sci. USA, 1997, 94, 10821-10826 (**Exhibit 4**);

20. Aharoni, et al., "Cop 1 Specific Supporessor Cells Inhibit Experimental Allergic Encephalomyelitis Induced by Either Mouse Spinal Cord Homogenate or Proteolipid Protein Peptide 139-151", Neurology, 1997, Vol. 48, No. 3, A422 (**Exhibit 5**);

21. Aharoni et al., "Bystander Suppression of Experimental Autoimmune Encephalomyelitis by T Cell Lines and Clones of the Th2 Type Induced by Copolymer 1", J. Neuroimmunol. 1998, 91(1-2), 135-146 (**Exhibit 6**);

22. Asakura et al., "A unique population of circulating autoantibodies promotes central nervous system remyelination", Multiple Sclerosis, 1998, 4, 217-221 (**Exhibit 7**);

23. Asakura et al., "Targeting of IgMk Antibodies to Oligodendrocytes Promotes CNS Remyelination", The Journal of Neuroscience, 1998, 18(19), 1700-1108 (**Exhibit 8**);

24. Bieber, et al., "Antibody-mediated remyelination: relevance to multiple sclerosis", Multiple Sclerosis, 2000, 6(2), S1-S5 (**Exhibit 9**);

25. Bieber, et al., "Humoral autoimmunity as a mediator of CNS repair", A Trends Guide to Neurodegenerative Disease and Repair/Review, 2001, 24(11), S39-S44 (**Exhibit 10**);

26. Duda, et al., "Human and Murine CD4 T Cell Reactivity to a Complex Antigen: Recognition of the Synthetic Random Polypeptide Glatiramer Acetate", The Journal of Immunology, 2000, 165, 7300-7307 (**Exhibit 11**);

27. Johnson, et al. "Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: results of a phase III multicenter, double-blind placebo-controlled trial. The Copolymer 1 Multiple Sclerosis Study Group", Neurology, 45(7), 1268 (abstract) (**Exhibit 12**);

28. Lovell, K. and Jones, M., "CNS Infections, Spongiform Encephalopathy and Demyelinating Diseases," Karol Marcinkowski U. Med. Sci., Dept. Pathol., Poland, last updated on 2003-04-20, <URL:http://ampat.amu.edu.pl/guzyuno/CNS_INFE.HTM> (**Exhibit 13**);

29. McGavern, et al. "Do Antibodies Stimulate Myelin Repair in Multiple Sclerosis?", The Neuroscientist, 1999, 5(1), 19-28 (**Exhibit 14**);

30. Merck Manual of Diagnosis and Therapy, Merck Research Laboratiories, Whitehouse Section, N.J., 17th Ed., 1999, 1300-1303, 1312-1317 (**Exhibit 15**);

31. Pavelko, et al., "Acceleration in the Rate of CNS Remyelination in Lysolecithin-Induced Demyelination", The Journal of Neuroscience, 1998 18(7), 2498-2505(**Exhibit 16**);

32. Physician's Desk Reference, 2000, Medical Economics Co. Inc., Montvale, NJ, 3115 (**Exhibit 17**);

33. Rodriguez, et al., "Neurological Therapeutics, 1998, 15(3): 245-250 (**Exhibit 18**);

34. Teva, et al., "Copolymer-1 Glatiramer Acetate Copaxone Agent for Multiple Sclerosis", Drugs of the Future, 1998, Vol. 23, No. 2, 213-214 (**Exhibit 19**);

35. Warrington, et al., "Human monoclonal antibodies reactive to oligodenrocytes promote remyelination in a model of multiple sclerosis", PNAS, 2000, 97(12), 6820-6825 (**Exhibit 20**);

36. Warrington, et al., "Immunoglobulin-mediated CNS repair", J. Allergy Clin. Immunol., 2001, S121-S125 (**Exhibit 21**);

37. Wiesemann, et al., "Glatiramer Acetate (GA) induces IL-13/IL-5 secretion in naïve T cells", Journal of Neuroimmunology, 2001, 119, 137-144 (**Exhibit 22**).

This Supplemental Information Disclosure Statement is being submitted after the issuance of a first Office Action on the merits in connection with the subject application but before the mailing date of any final action. Accordingly, a fee of $180.00 is required and a check in that amount is enclosed. This Supplemental Information Disclosure Statement shall be considered pursuant to 37 C.F.R. §1.97(c)(2).

Applicants request that the Examiner review the publications and make them of record in the subject application.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee, other than the enclosed fee of $180.00 is deemed necessary in connection with the filing of this Amendment and Second Supplemental Information Disclosure Statement. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Gary J. Gershik 3/24/05

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